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Review article

Phytosomes as Novel Drug Delivery System for Herbal Medicine –A Review

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ABSTRACT
Phytomedicines, complex chemical mixtures prepared from plants, have been used for health maintenance since ancient times. But many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken orally. The term "phyto" means plant while "some" means cell-like. Phytosomes are little cell like structure. This is advanced forms of herbal formulations which contains the bioactive phytoconsituents of herb extract surrounds and bound by a lipid. Most of the bioactive constituents of phytomedicines are water-soluble compounds like flavonoids, glycosides; terpenoids in which flavonoids are a major class of bioactive compounds possesses broad therapeutic activities. Because of water soluble herbal extract and lipophilic outer layer phytosomes shows better absorption and as a result produce better bioavailability and actions than the conventional herbal extracts containing dosage form. Phytosomes are produced by a process where by the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine producing a lipidcompatible molecular complex. This study reveals that phytosome exhibit better pharmacokinetic and pharmacodynamics profile than conventional herbal extracts.
Key words: Phytosomes, Herbal medicine, Novel Drug Delivery System.

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INTRODUCTION

Over the past century, phytochemical and phyto-pharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, glycosidic aglycones etc) are poorly absorbed either due to their large moleculer size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability.[1] The Phytosome process produces a little cell because of that the valuable components of the herbal extract are protected from destruction by digestive secretions and gut bacteria. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. Most of the bioactive constituents of phytomedicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle). However, many flavonoids are poorly absorbed; the poor absorption of flavonoid nutrients is likely due to two factors. First, they are having multiple-ring molecules that are too large to be absorbed by simple diffusion. Secondly, flavonoid molecules typically have poor miscibility with oils and other lipids, which limited their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Water soluble flavonoid molecules can be converted into lipid-compatible molecular complexes; aptly called phytosomes.[2] These are better able to transition from the water phase external to the enterocyte, into the lipid phase of its outer cell membrane and from there into the cell, finally reaching the blood.[1] The lipid-phase substances that Indena successfully employed to make flavonoids lipid-compatible are phospholipids from soy, mainly phosphatidylcholine (PC). PC is miscible both in the water phase and in oil/lipid phases, and is excellently absorbed when taken by mouth. PC is the principal molecular building block for cell membranes and the molecular properties that suit PC for this role also render it close to ideal for its PHYTOSOME Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one PC molecule. A bond is formed between the two molecules to create a hybrid molecule. This hybrid is highly lipid-miscible, better suited to merge into the lipid phase of the enterocyte's outer cell membrane (Figure 1). Once there it can cross the enterocyte and reach the circulating blood. Phosphatidylcholine is not merely a passive "carrier" for the bioactive flavonoids of the phytosomes, but a bioactive nutrient with documented clinical usefulness.The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial PC intakes. Phytosomes are not liposomes— structurally, the two are distinctly as shown in Figure 2.

The phytosome is a unit of a few molecules bonded together, while the liposome is an aggregate of many phospholipids molecules that can enclose other phytoactive molecules but without specifically bonding to them. Liposomes are touted delivery vehicles, but for dietary supplements their promise has not been fulfilled. But for Indena's phytosome products numerous studies prove they are markedly better absorbed and have substantially greater clinical efficacy. The PHYTOSOMETM technology is a breakthrough model for:

- Significantly greater clinical benefit.
- Assured delivery to the tissues.
- No compromise of nutrient safety.
- Marked enhancement of bioavailability.[3]

Principle

Phosphatidylcholine (or phosphatidylser- ine) is a bifunctional compound. The phosphatidyl moiety is lipophilic and the choline (serine) moiety is hydrophilic in nature. This dual solubility of the phospholipid makes it an effective emulsifier. Thus, the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then surrounds the choline bound material. Hence, the phytoconstituents produce a lip-

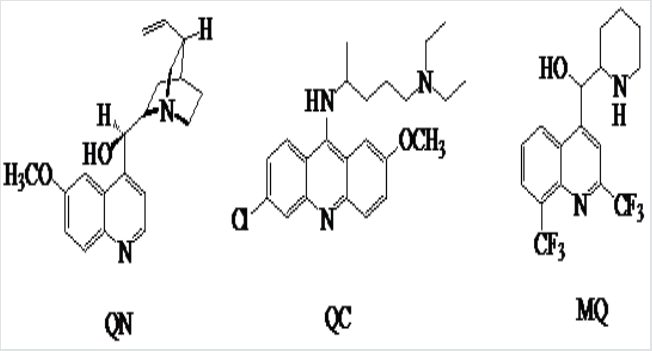

Figure 1: Schematic reprsentation of Phytosomes.[19]

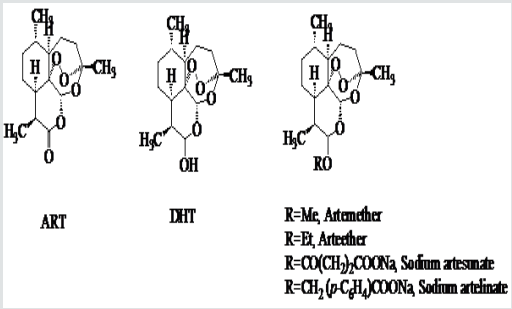

Figure 2: Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment).[19]

id compatible molecular complex with phospholipids, as shown (also called as phy- tophospholipid complex).

Properties of phytosomes

1) Physico Chemical properties:

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipids and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipids-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomal-like structures. In liposomes the active principle is dissolved in the internal pocket or it is floating in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane. For example in the case of the catechindistearoylphosphatidylcholine complex, there is the formation of H-bonds between the phenolic hydroxyl ends of the flavones moiety and the phosphate ion on the phosphatidylcholine moiety. Phosphatidyl choline can be deduced from the comparison of 1H-NMR and 13C-NMR spectra of the complex with those of the pure precursors. The signals of fatty chain remain almost unchanged. Such evidence inferred that the too long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and flavanoid molecule and enables the complex to dissolve in low polarity solvents.[4]

2) Biological properties

Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts. The increased bioavailability of the phytosome over the non complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects.[5]

Strength of phytosomes

Phytosomes show better stability as chemical bond is formed between phsospholipid molecule and phytocon- stituent(s).

Dose of phytoconstituents is reduced due to more bioavailability of the phytoconstituents in the complex form.[1] Duration of action is increased.

Phytoconstituents complex with phospholipids are more stable in gastric sections and resist the action of gut bacteria.

Enhanced permeability of phytoconstituents across the biological membranes.

Absorption of lipid insoluble polar phyto- constituents through different routes shows better absorption, hence shows significantly higher therapeutic effects.

Phoshatidylcholine used in the formation of phytosomes, besides acting as a carrier also possess several therapeutic properties, hence gives the synergistic effect when particular substance is given.

Drug entrapment is not a problem with phytosome as the complex is biodegradable.[6,7,8,9,10]

Advantages of phytosomes[11,12]

Phytosomes have the following advantages

1) It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.

2) Appreciable drug entrapment.

3) As the absorption of active constituent (s) is improved, its dose requirement is also reduced.

4) Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.

5) Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.

6) Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as functional cosmetics. Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means.

Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. Most of the phytosomal studies are focused to Silybum marianum (milk thistle) which contains premier liver protectant flavonoids. The fruit of the milk thistle plant contains flavonoids known for hepatoprotective effects.[13,14]

Tedesco *et al.* Reported silymarin phytosome show better anti hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks.[15]

Busby *et al.* reported that the use of a silymarin phytosome showed a better foetoprotectant activity from ethanolinduced behavioural deficits than uncomplexed silymarin.[16]

Grange *et al.* conducted a series of studies on silymarin phytosome, containing a standardized extract from the seeds of S. marianum, administered orally and found that it could protect the foetus from maternally ingested ethanol.[17]

Moscarella *et al.* investigated in one study of 232 patients with

chronic hepatitis (viral,alcohol or drug induced) treated with silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver function returned to normal, faster in patients taking silybin phytosome compared to a group of controls[18].

CONCLUSION

Absorption of phytosome in gastro intestinal tract is appreciably greater resulting in increased plasma level than the individual component. Complex formation ratio of component and phospholipids is 1:1 and 2:1. Phytosomes are used as a medicament and have wide scope in cosmeticology. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application. Phytosomes forms a bridge between the conventional delivery system and novel delivery system.

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